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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

FITZPATRICKS
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ROYAUME-UNI

Date of mailing *(day/month/year)* 09 October 2003 (09.10.03)	
Applicant's or agent's file reference 32/64087WO	**IMPORTANT NOTICE**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB03/01404	31 March 2003 (31.03.03)	02 April 2002 (02.04.02)

Applicant
NORBROOK LABORATORIES LIMITED

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

   AU, AZ, BY, CH, CN, CO, DE, DZ, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

   AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-*bis*)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 09 October 2003 (09.10.03) under No. 03/082340

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

   The applicable time limit for entering the national phase will, **subject to what is said in the following paragraph,** be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

   In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   For filing a **demand for international preliminary examination**, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

   It is the applicant's **sole responsibility** to monitor all these time limits.

   The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

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CONFIRMATION BY MAIL

Our Reference	Your Reference	Date
32/64087WO		10 November 2003

Dear Sirs

International (PCT) Patent Application No. PCT/GB03/01404
Injectable Veterinary Composition for Small Animals
in the name of Norbrook Laboratories Limited

We refer to the communication dated 10th September 2003 notifying the applicant of the outcome of the International Search.

Please find enclosed herewith amended claims 1-21 to replace those currently on file. The claims have been amended to restrict them to a physiologically active salt of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) and a poloxamer wherein said injectable aqueous composition is stable at room temperature. Where originally there were 24 claims after amendment there are now 21. Claim 1 was amended and claims 2 and 3 were cancelled to be replaced by new claim 2 and previous claim 14 became new claim 3. Claims 6, 7, 9, 17 have been amended in line with claim 1 above. Claims 10, 14 (now 3) and 24 were cancelled. All other claims were renumbered and their dependencies amended where necessary to take account of the cancelled claims.

EP0955063 (D1) describes the use of an aqueous composition for subcutaneously or intramuscularly administering drug formulations. The composition comprises a combination of a polyoxyethylene-polyoxypropylene (Copolymer (A)) with a weight average molecular weight of 8000 to 20000; and a polyoxyethylene-polyoxypropylene (Copolymer (B)) with a weight average molecular weight of 4000 to 8000. The composition is described as being useful for the subcutaneous or intramuscular administration of various agents with the advantage being stated that the composition is liquid at room temperature but when administered forms a depot gel, allowing controlled release of the pharmaceutical compounds.

D1 also states that the use of poloxamer is well known to be useful in the manufacture of pharmaceutical preparations but these compounds in solution may also be stabilised by the presence of BHT, see page 2

lines 46 to 48 of D1. In summary D1 teaches the combined use of both Copolymer A and Copolymer B for the production of improved pharmaceutical preparations with sol-gel transitional properties, in relation to temperature dependent viscosity and penetration resistance, page 4 lines 16 to 18, examples 1 to 16 and figures 1-4 of D1.

The amended claims set enclosed herewith is both novel and inventive over D1, as D1 does not refer to any advantage of increased room temperature stability of a sol-gel type of pharmaceutical preparation by the inclusion of poloxamers in the disclosed manner. The only reference in D1 to temperature is that the sol-gel transitional temperature is between 20 and 40°C, which facilitates sustained release of the drug being administered at body temperature, see page 5 lines 54 to 57.

US5283067 (D2) describes a dry formulation obtainable by lyophilisation, which is suitable for the preparation of a stable, aqueous suspension for the parenteral administration of a diclofenac salt. The dry formulation contains a pharmaceutically acceptable and micronised salt of diclofenac and optional pharmaceutically acceptable adjuvants. It also indicates that poloxamers are useful wetting agents or surfactants for the re-suspension of lyophilised diclofenac based pharmaceutical preparations for parenteral or intramuscular injection, see column 2 line 65 to column 3 line 11. Lyophilisation of such preparations allows for storage of these preparations at room temperature. When required for use are they re-suspended in the desired buffer.

The amended claims set enclosed herewith is both novel and inventive over D2 as D2 does not refer to poloxamers as being useful for the long-term stabilisation of pharmaceutical preparations at room temperature, nor does it refer to poloxamers as being useful in the reduction of inflammation upon injection of Carprofen or any other NSAID.

Finally CH663788 (D3) describes new salts of carprofen namely 6-chloro-α-methylcarbazol-2 acid with a basic α-amino acid, either L-Lysine or L-Arginine, but preferably L-Lysine. The advantages of the salts described in this document are indicated as being that NSAID is rendered more soluble and suitable for parenteral administration (Claims 1 to 6 and page 2 lines 41 to 48) as well as having 40% more bio-availability in blood plasma when compared to injection of Carprofen alone in solution, page 2 lines 10 to 16. D3 comments on the suitability of carrier molecules like gelatine, starch, magnesium stereate and polyalkylene glycols for facilitating the administration of the NSAID in a pharmaceutical preparation, page 2, column 2 and lines 29 to 36. It also teaches use of a poloxamer as a suppository base for the administration of Carprofen-Lysitiate.

However, importantly D3 neither describes nor teaches in any way, the usefulness of poloxamers in solution and how they might increase the room temperature stability of pharmaceutical preparations containing Carprofen or salts thereof. Thus again the amended claims set is both novel and inventive over the teachings of D3.

Accordingly we believe that the enclosed amended claims1-21 are both novel and inventive over all the cited art either alone or in combination.

Yours faithfully
FITZPATRICKS

Enc: Claims 1 to 21 rj

Amendment under Article 19(1) PCT

CLAIMS

1. An injectable aqueous composition for veterinary use containing a physiologically active salt of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) in an amount of from about 0.5 to 30% (w/v) together with a poloxamer in an amount of from about 0.5 to 20% (w/v) and said injectable aqueous composition being stable at room temperature.

2. An injectable aqueous composition according to Claim 1 wherein said composition is room temperature stable for a minimum of 11 months.

3. An injectable aqueous composition according to Claims 1 or 2 wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH2CH2)_zH$ wherein x is about 75, y is about 30 and z is about 75 or x is 98, y is 67 and z is 98.

4. An injectable aqueous composition according to Claim 1 wherein the carprofen salt is in the form of an arginine salt.

5. An injectable aqueous composition according to Claim 1 wherein the carprofen salt is in the form of a lysine salt.

6. An injectable aqueous composition according to any one of Claims 1 to 5 wherein the carprofen is present in an amount of from about 2.5 to 7.5% (w/v).

7. An injectable aqueous composition according to any one of Claims 1 to 5 wherein the carprofen is present in an amount of from about 2.5 to 5% (w/v).

8. An injectable aqueous composition according to any one of Claims 1-7 comprising arginine in an amount of from about 1 to 20% (w/v).

9. An injectable aqueous composition for veterinary use containing a physiologically active salt of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid),

in an amount of from at least about 0.25% (w/v) together with a poloxmer in an amount from about 0.5 to 20% (w/v).

10. An injectable aqueous composition according to Claim 9 wherein the poloxamers are present in an amount of from about 2 to 12% (w/v).

11. An injectable aqueous composition according to Claim 9 wherein an organic solvent is present with the poloxamer.

12. An injectable aqueous composition according to Claim 11 wherein the organic solvent is present in the range of 0.5 to 20% (w/v).

13. An injectable aqueous composition according to Claims 11 or 12 wherein the poloxamers are present in an amount of from 1% to 12% (w/v).

14. An injectable aqueous composition for veterinary use containing from about 0.25% to 30% (w/v) of carprofen arginine salt together with a poloxamer in an amount from about 0.5 to 20% (w/v).

15. An injectable aqueous composition for veterinary use according to claim 14 comprising arginine in an amount of from 1 to 20% (w/v).

16. An aqueous injectable composition comprising carprofen or a physiologically acceptable salt thereof in an amount of from 0.25% to 30% (w/v), a polymeric species selected from the group of polyoxypropylene/polyoxyethylene block co-polymers in the amount of from 0.5% to 20% (w/v), a preservative and water sufficient for injection.

17. A method of producing a room-temperature stable injectable aqueous composition for veterinary use comprising bringing together an effective amount of carprofen or a physiologically acceptable salt thereof and a poloxamer, and adding sufficient water for injection.

18. A method according to Claim 17 wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ wherein x is about 75, y is about 30 and z is about 75.

19. A method of producing an injectable aqueous composition according to Claims 17 or 18 wherein said method further comprises the inclusion of a preservative.

20. An injectable aqueous composition for veterinary use according to any one of the Examples 1 to 19 hereinbefore.

21. A method of producing an injectable aqueous composition substantially as described in the Example 1.